

The role of Fas and related death receptors in autoimmune and other disease states

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The Fas receptor, also known as APO-1 or CD95, has emerged as a key initiator of apoptotic programmed cell death in a variety of cell types. CD4⁺ T cells are unique in their ability to commit "suicide" by stimulating their own Fas receptors with secreted or membrane-bound Fas ligand. This takes place in the setting of repeated stimulation with T-cell antigens and is thought to be a mechanism for controlling the expansion of T cells during viral infections and autoimmune disease states. T cells can also trigger apoptosis in B cells, macrophages, and other cell types through Fas ligand. These interactions negatively regulate the immune system but can also contribute to immunopathology, as occurs in Fas-mediated damage of target tissues in hepatitis and other organ-specific autoimmune diseases. The dual role of Fas in the immune response complicates the understanding of its role in disease states and may limit its potential as a therapeutic target. Despite the many roles of Fas in immunoregulation, findings in experimental mouse strains and human patients with genetic deficiencies in the Fas pathway have shown that the main result of disrupting this pathway *in vivo* is systemic autoimmunity and a predisposition toward lymphoid malignancies. The role of Fas in various cell types and the lessons we have learned from Fas-deficient patients with the autoimmune lymphoproliferative syndrome will be discussed. (*J Allergy Clin Immunol* 1999;103:729-38.)

Key words: Fas, APO-1, CD95, autoimmune lymphoproliferative syndrome, autoimmunity, therapy, lymphocytes, apoptosis

FAS AND OTHER DEATH RECEPTORS IN THE IMMUNE RESPONSE

Fas/CD95: A death receptor in the TNF-receptor superfamily

The Fas receptor was first identified by antibodies that induced rapid cell death. Treatment of susceptible cells with these antibodies induced all the hallmarks of apop-

Abbreviations used

ALPS: Autoimmune lymphoproliferative syndrome
DED: Death-effector domain
TCR: T-cell receptor

toxis (ie, programmed cell death), a process originally defined in cells dying during normal development or after induction with chemotherapeutic agents, glucocorticoids, or γ -irradiation.¹ Unlike cells dying by necrosis, in which the intracellular contents of the cell are released into the environment after membrane rupture, apoptosis involves the orderly destruction and packaging of cellular contents into apoptotic blebs, which are rapidly recognized and phagocytosed by cells of the reticuloendothelial system. The orderly disassembly of the cell is carried out by a specialized set of intracellular proteases, the caspases, which cleave key structural and regulatory protein substrates, culminating in the cleavage of DNA into small oligonucleosomal fragments.² The packaging and phagocytosis of cellular contents in apoptosis is thought to result in less uncontrolled inflammation than that found in necrosis, although as will be discussed, the Fas receptor and related molecules can also induce proinflammatory responses.

Cloning of the Fas receptor revealed a 44-kd type-1 membrane glycoprotein in the TNF-receptor superfamily.^{3,4} Like other members of this family, the Fas receptor is characterized by cysteine repeat domains in its extracellular region. In addition, an 80 amino acid region of the intracellular portion with homology to a similar domain in TNFR1 was found and was named the *death domain* because mutations in this area abrogated apoptosis induction after surface cross-linking of the receptor.⁵ The ligand for the Fas receptor was identified as a trimeric type-II membrane protein resembling other TNF family members that can be secreted after cleavage from the membrane by metalloproteinases.^{6,7} Four other human TNFR superfamily receptors with death domains, TNFR1, DR3, DR4, and DR5, have been found thus far.⁸⁻¹⁵ The term *death receptor* has been used to group these TNF family receptors with death domains because they share the ability to directly initiate apoptosis. The ligand for DR4 and DR5 is the TNF family

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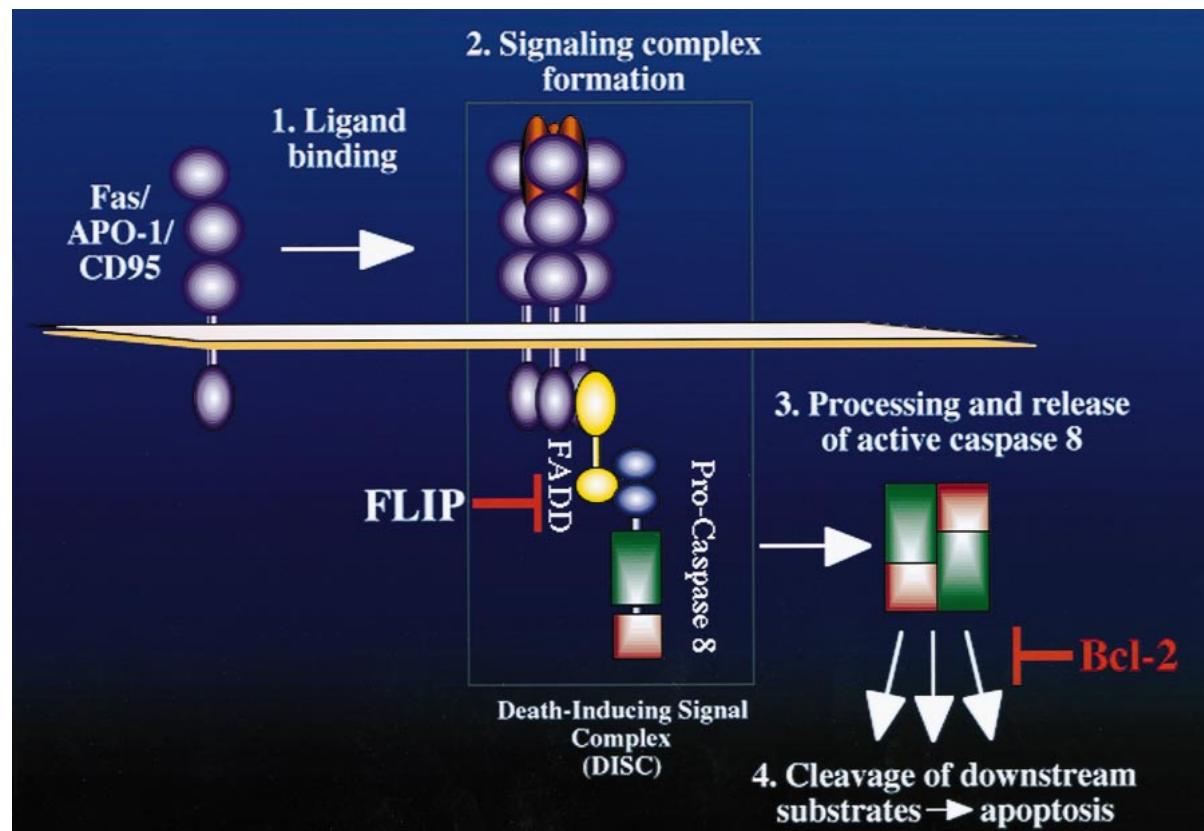


FIG 1. Signaling by the Fas death receptor. The major steps in initiation of the apoptosis pathway by the Fas receptor are shown. The purple spheres in the extracellular region of the Fas receptor schematic indicate cysteine-repeat domains of the receptor. The oval spheres indicate the death domains in Fas and FADD. Negative regulatory proteins described in the text are shown in red.

member TRAIL, and another TNF family member, TRANCE, was identified as a ligand for DR3. Secreted forms of most of these receptors can be produced by alternative splicing or proteolytic cleavage from the plasma membrane. In addition, 2 genes encoding truncated TRAIL receptors have also been identified, which function as antagonists of TRAIL signaling.^{14,16-18} Secreted and truncated forms of many death receptors have been found to block receptor function and have been used as therapeutic agents in the TNF system. The function of the Fas receptor in vivo was clarified when it was found that the recessive *lpr* mutation in mice, which causes systemic autoimmunity similar to that seen in human SLE, was caused by a mutation in the gene for the Fas receptor that prevents normal protein production.¹⁹ A similar murine syndrome, *gld*, was found to be caused by a point mutation in the Fas ligand gene.²⁰

Much progress has been made in identifying the intracellular mediators of death receptor signaling, particularly for the Fas receptor (Fig 1). Unlike other signaling systems, recruitment and activation of intracellular mediators apparently does not require any biochemical modifications, such as phosphorylation or release of second messengers, but instead relies on protein-protein associations through a series of related structural

modules. Binding of Fas ligand or stimulation with agonistic antibodies leads to aggregation of the receptor on the cell membrane and specific recruitment of intracellular signaling molecules, known as the death-inducing signal complex or DISC.²¹ The FADD adapter protein binds to the intracellular death domain of Fas through a homologous death domain.^{22,23} The FADD protein also codes for a related module, the death-effector domain (DED), at the N-terminus. The DED was originally defined by its ability to induce apoptosis after overexpression in a number of cell types. It is an 80 amino acid motif structurally similar to the death domain.²⁴ Through the DED, FADD was found to recruit the cysteine protease caspase-8 to the Fas-signaling complex.^{25,26} The identification of caspase-8 (also known as FLICE or MACH) in the Fas-signaling complex was a major advance because it directly linked the Fas receptor to the action of caspases. Proteases in this family cleave substrate proteins after aspartate residues and produce many of the phenotypic features of apoptosis through cleavage of structural and regulatory proteins within the cell.² In some cell types Fas-induced cell death is also dependent on an alternate pathway involving mitochondrial permeability transition and proapoptotic bcl-2 family members.²⁷

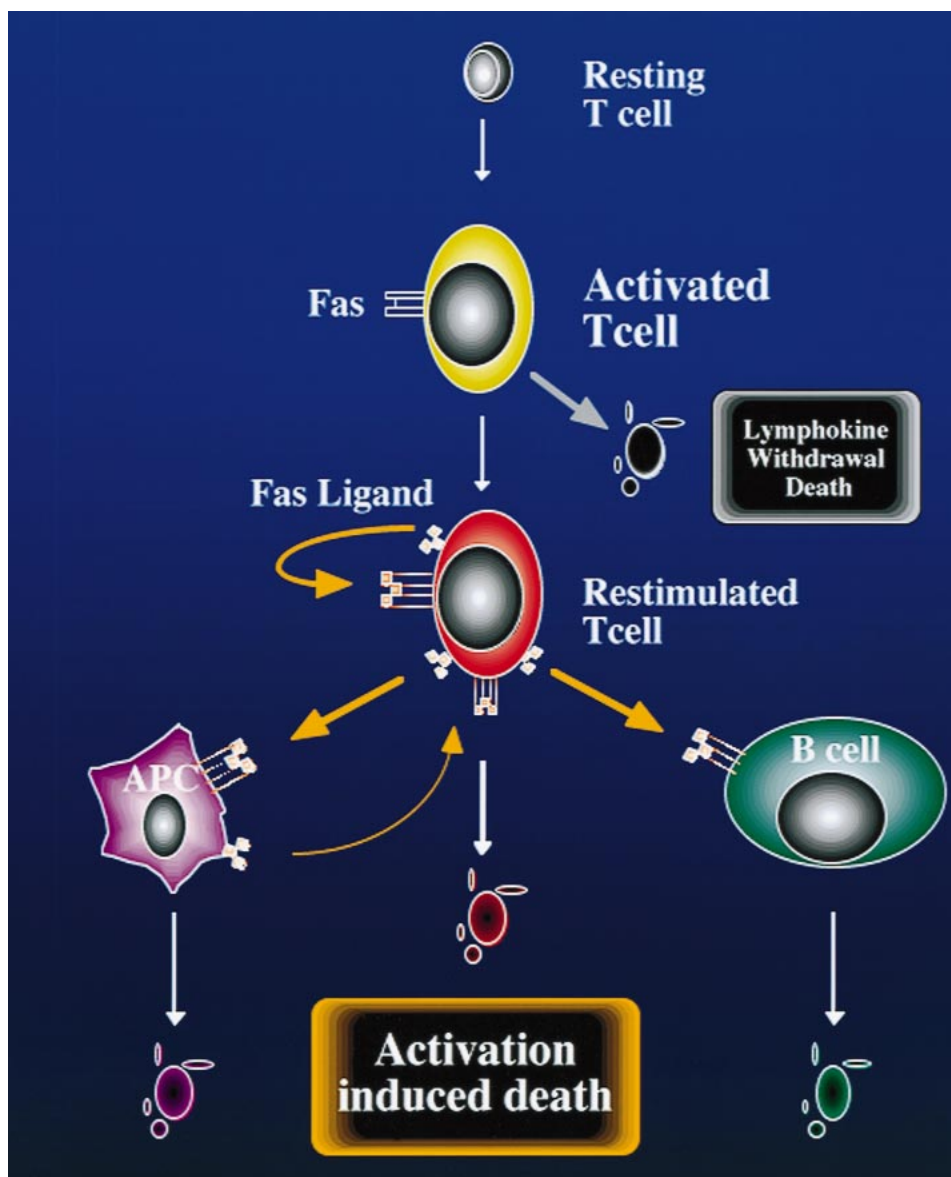


FIG 2. The role of Fas and Fas ligand in the immune response. T-cell activation is depicted in the center of the figure, with antigen stimulation driving resting T cells (grey cell) into the cell cycle (yellow cell). Restimulation through the T-cell antigen receptor leads to expression of Fas ligand and sensitivity to apoptosis through the Fas receptor (red cell). Fas-mediated killing of B cells and antigen-presenting cells (APC) is illustrated, as well as the possible killing of T cells by APCs.

After recruitment to the receptor, caspase-8, which is synthesized in an inactive proform, undergoes autocatalytic processing to produce an active caspase-8 protease. The main function of the Fas-signaling complex seems to be activation of caspase-8 because transfection of active caspase-8 can induce all of the hallmarks of apoptosis.^{25,28} Moreover, oligomerization of active caspase-8 can itself induce apoptosis, replacing the function of CD95 and FADD.^{29,30} Thymocytes and embryonic fibroblasts from FADD-deficient mice are also resistant to Fas-induced apoptosis, showing the essential role of this pathway in mediating apoptosis.^{13,31}

Cell type-specific regulation of Fas signaling

With such an important role in cell death, it is not surprising that the regulation of Fas signaling is highly complex. An emerging theme in research on this topic is the concept that regulation of Fas signaling is specific to the cell type and stage of development. Developing T cells in the thymus express Fas and can undergo apoptosis after Fas cross-linking. However, the Fas molecule is apparently not required for the clonal deletion of autoreactive T cells in the thymus because Fas- or Fas ligand-deficient mice appropriately delete autoreactive T cells.^{32,33}

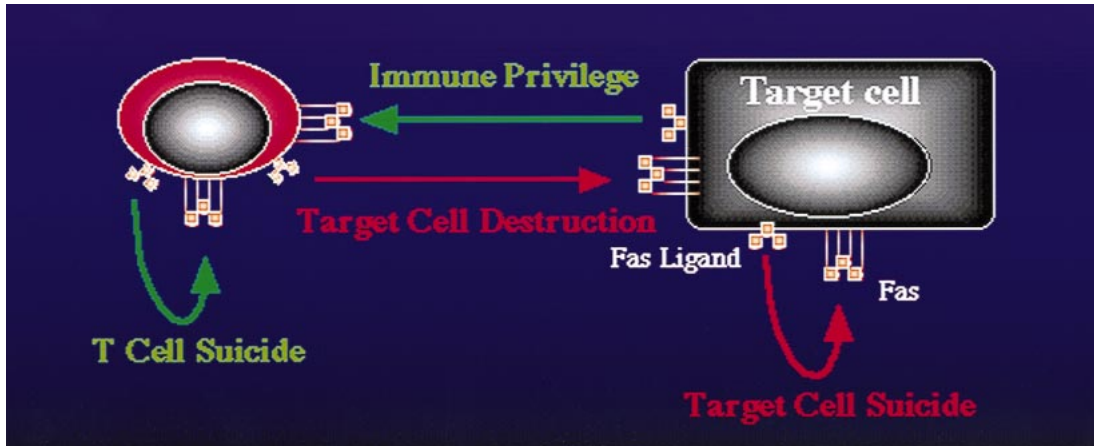


FIG 3. The role of the Fas system in T cell/target cell interactions. The 4 possible outcomes of Fas/Fas ligand interactions between T cells and nonimmune cells are depicted. Note that interactions may be enhanced by recognition of antigens presented by the target cell by the T-cell antigen receptor (not shown). Target cell killing results from ligation of Fas on target cells. Immune privilege is thought to result from the opposite interaction, killing of T cells through engagement of their Fas receptors by Fas ligand from the target cell, although other factors may be necessary for this to occur (see text). Both T cells and target cells can commit suicide through autocrine Fas/Fas ligand stimulation. Interactions that would enhance inflammation and autoimmune disease are shown in red, and negative regulatory interactions are shown in green.

In mature T cells the Fas pathway has an important role in autocrine "suicide" of excess effector cells (Fig 2). Resting naive T cells express little surface Fas, and most studies have found them to be resistant to the cytotoxic effects of Fas ligand or anti-Fas antibodies. After activation through the T-cell receptor (TCR), Fas surface expression is upregulated, with maximal levels reached after 5 days.³⁴ However, activated T cells are relatively resistant to the cytotoxic effects of Fas signaling until they have been cultured under growth conditions for at least 1 week.³⁵ This block has been shown to correlate with lack of recruitment of the FLICE/caspase-8 protein to the Fas-signaling complex. This may be related to the increased expression of the negative regulatory FLICE-like inhibitory protein (FLIP), which can bind to caspase-8 through homologous DEDs and caspase domains.³⁶ The delay in sensitivity to apoptosis may be important in allowing the expansion of antigen-specific T cells during an immune response.

After restimulation through the TCR, both murine and human activated T cells become more sensitive to Fas-induced apoptosis. The mechanism for this "competency to die" signal is not clear, but it can be mimicked by signaling through the TCR ζ -chain alone or through altered peptide ligands, which do not elicit full T-cell responses.^{37,38} These processes limit T-cell suicide to those cells responding to stimulatory ligands within a mixed population of cells. Mixing studies have shown that bystander-activated T cells will not efficiently undergo apoptosis in the presence of recently restimulated T cells despite the synthesis of active Fas ligand by all the cells in the culture.³⁹ In an inflammatory infiltrate this mechanism may allow elimination of potentially autoreactive cells while leaving bystander cells intact. In the setting of a chronic viral infection, such as HIV, this mechanism may also play a role in the elimination of virus-specific T cells.

Within T-cell subsets, there are some differences in the death cytokines used and in the sensitivity to autocrine cell death. Although most of the TCR-induced apoptosis in CD4 cells is dependent on the Fas receptor engagement, CD8 T cells, at least in the mouse, appear to preferentially use the TNF pathway.⁴⁰ T_{H2} T cells also appear to be less sensitive to Fas-mediated apoptosis than are T_{H1} cells.⁴¹ Receptor-induced apoptosis is not the only mechanism resulting in activated T-cell apoptosis. Although receptor-induced apoptosis requires the continuous presence of IL-2, withdrawal of trophic cytokines, such as IL-2, will result in T-cell apoptosis in a Fas- and TNF receptor-independent fashion.⁴² This "passive" lymphokine withdrawal death may be more important in reducing the numbers of T cells after acute stimuli such as the polyclonal activation in response to superantigens.⁴³

Like T cells, Fas-deficient B cells can escape self-tolerance. Studies with chimeric mice have shown that only Fas-deficient B cells from *lpr* mice produce autoantibodies.⁴⁴ However, mature B cells do not undergo Fas-mediated suicide after B cell antigen-receptor engagement. Instead, it appears that the type of antigen stimulation governs whether a B cell can become a target for Fas-mediated killing by T cells. As in T cells, Fas is not required for elimination of autoimmune B cells during maturation.⁴⁵ A subset of autoreactive B cells do mature but become functionally inactive, with defective antigen receptor signaling and no secretion of autoantibodies.⁴⁶ When these cells mature or are transferred into a mouse deficient in Fas or Fas ligand in the presence of T cells reactive against the same antigens, tolerance can be reversed, and potentially pathogenic autoantibodies are produced. Normally, T cells can eliminate self-reactive peripheral B cells through a mechanism requiring Fas

and another member of the TNF superfamily, CD40, on B cells.⁴⁷ In addition, signaling through surface immunoglobulin in nontolerant B cells delivers a separate signal that may protect them from Fas-mediated apoptosis.^{48,49}

Regulation of the Fas pathway is not as clear for the monocyte-derived antigen-presenting cells, although some of the same principles may apply. Peripheral blood monocytes spontaneously undergo apoptosis, some of which may be mediated by Fas.⁵⁰ Differentiated tissue macrophages continue to express Fas but appear to be more resistant to apoptosis induced by Fas cross-linking.^{50,51} Blood-derived human dendritic cells are also sensitive to Fas-induced apoptosis, but CD40 signals protect these cells from Fas-induced death.⁵² This suggests that dendritic cells successfully presenting antigen to T cells during an immune response may be selectively rescued from apoptosis. Some types of dendritic cells have also been found to express Fas ligand, making it possible that these cells can also induce the apoptosis of responding T cells.⁵³⁻⁵⁵

The Fas receptor is widely expressed outside the immune system, where it may play a role in T cell-mediated immunopathology (Fig 3). In mesodermal cells, such as fibroblasts, Fas surface expression was found to be upregulated by DNA damage and other stimuli that upregulate p53.⁵⁶ Among nonhematopoietic cells, hepatocytes appear to be uniquely sensitive to the apoptosis-inducing effects of Fas stimulation. Indeed, the major toxicity of agonistic anti-Fas antibodies is liver failure caused by massive hepatocyte apoptosis. In a viral hepatitis model, in which most of the liver damage is caused by the lymphocyte response against hepatocytes expressing viral antigens, Fas-deficient animals were found to be resistant to liver injury, illustrating the critical role of Fas in hepatocyte injury.⁵⁷⁻⁵⁹

The expression of Fas ligand on nonimmune cells can also induce apoptosis in responding lymphocytes. This phenomenon has been used to explain the induction of immune tolerance to these tissues, which has been termed *immune privilege*. Expression of Fas ligand in the anterior chamber of the eye and in the testis has been found to be critical for induction of tolerance to tissue-specific antigens in these organs.^{60,61} However, experiments with Fas ligand expression in other cell types have led to different results, with some studies finding tolerance induction but others finding a neutrophilic infiltrate into Fas ligand-expressing tissues and a lack of tolerance.⁶²⁻⁶⁵ A recent study found that environmental factors, particularly the cytokine transforming growth factor- β , may shift the balance toward immune privilege by blocking neutrophil activation in response to Fas ligand stimulation.⁶⁶

THE ROLE OF FAS/FAS LIGAND INTERACTIONS IN AUTOIMMUNE AND OTHER DISEASE STATES

The role of the Fas receptor in regulating the human immune response and in the evolution of clinical disease

TABLE I. Involvement of the Fas/Fas ligand system in human diseases

Disease state	Pathway affected	Proposed mechanism
ALPS	Impaired T-cell suicide	Fas mutations
Autoimmune thyroid disease	Enhanced target cell suicide	Expression of Fas ligand on thyrocytes
Hypereosinophilia	Impaired eosinophil apoptosis	Cytokine or somatic mutations
Viral hepatitis	Enhanced target cell killing	T-cell engagement of Fas on hepatocytes
Malignancies expressing Fas ligand	Enhanced T-cell killing (immune privilege)	Induced apoptosis of T cells by malignant target cells
Fas-resistant malignancies	Impaired tumor cell killing	Decoy receptors, Fas mutations on tumor cell

is being actively investigated. The recent identification of the autoimmune lymphoproliferative syndrome (ALPS) as a disorder of defective lymphocyte apoptosis provides definitive evidence that directly links Fas receptor dysfunction with specific clinical and laboratory findings. Altered Fas or Fas ligand function may contribute to other human autoimmune, infectious, and malignant diseases as well (summarized in Table I). ALPS is characterized clinically by massive lymphadenopathy and splenomegaly, which typically is first seen in childhood.^{67,68} Accompanying these clinical findings is autoimmune hematologic disease, such as hemolytic anemia, thrombocytopenia, or both. In addition, patients with ALPS have markedly increased levels of circulating CD3 double negative T cells (ie, T cells negative for both CD4 and CD8). These cells express the α/β form of the antigen receptor and are normally found at very low levels (<1%) in the peripheral blood (Fig 4). Many patients with ALPS also have increased levels of circulating B cells together with a polyclonal hypergammaglobulinemia. These findings are similar to those found in Fas- or Fas ligand-deficient *lpr* and *gld* mouse strains.⁶⁹ The major difference between human patients and the animal model is that mice have multiorgan autoimmune disease with renal involvement, whereas autoimmune cytopenia predominates in ALPS. Studies of lymphocytes from patients with ALPS documented defective in vitro apoptosis by using activated T cells exposed either to anti-Fas antibodies or restimulation of the TCR with antibody to CD3.^{68,70} B-cell lines derived from the patients with ALPS were also shown to have a defect in Fas-mediated apoptosis.

The functional similarities between ALPS and the murine models directed investigation into possible abnormalities in either Fas or Fas ligand. These studies established that the majority of patients with ALPS have a mutation in the *APT1* gene encoding Fas.^{70,71} A variety of abnormalities have been characterized involving *APT1* exons that affect both the extracellular domains (exons 1

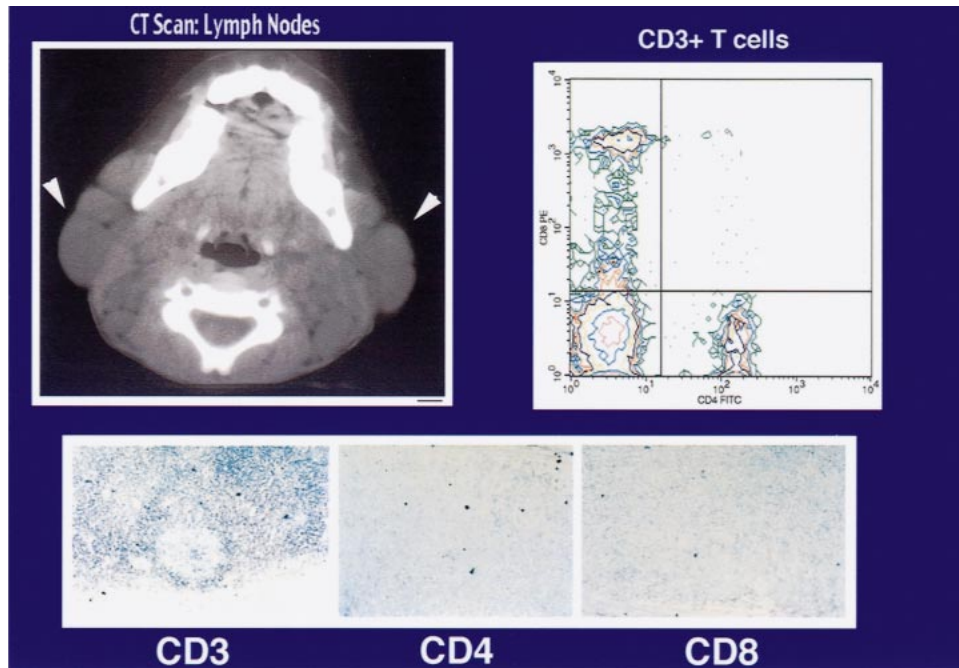


FIG 4. Clinical manifestations of ALPS. A computed tomography scan of the neck is shown at the top left, demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. The top right panel shows flow-cytometric analysis of peripheral blood T cells from a patient with ALPS, with CD8 expression on the vertical axis and CD4 on the horizontal axis. The lower left quadrant contains CD4⁺CD8⁺ cells, which are usually present as less than 1% of T cells expressing the $\alpha\beta$ TCR. The bottom panels show CD3, CD4, and CD8 staining (blue) on serial sections of a lymph node biopsy specimen from a patient with ALPS and also shows the large numbers of CD3⁺CD4⁺CD8⁺ T cells present in the interfollicular areas of the lymph node.

to 6) and the intracellular coding regions (exons 7 to 9). A major distinction between the human disorder and the murine model is that patients with ALPS have only heterozygous *APT1* mutations, whereas the disease in *lpr* mice requires a homozygous mutation.¹⁹ Proof that the *APT1* mutations were directly linked to the apoptotic defect was established by transfection experiments. In these studies a murine cell line that did not express human Fas was transfected with either normal (wild-type) or mutant (patient) DNA. This resulted in similar cell surface expression of human Fas with either normal or patient DNA. However, the addition of anti-Fas antibody induced apoptosis in murine cells expressing normal Fas but not in those that expressed mutant Fas. These data established that the mutations seen in the patients with ALPS are sufficient to produce an abnormality in Fas-mediated apoptosis. When combinations of normal and patient Fas DNA were transfected into the murine cell line, producing a mixture of normal and mutant human Fas receptors on the cell surface, Fas-induced apoptosis was impaired, demonstrating dominant negative interference by these heterozygous Fas mutations.⁷⁰ In addition, studies of Fas signaling in cells from patients with ALPS have shown a greater than 50% reduction in recruitment of the signaling proteins FADD and caspase-8 to the Fas receptor after receptor cross-linking. This suggests that the dominant-negative effect of Fas muta-

tions in ALPS occurs at the earliest steps of signal transduction.⁷²

Despite the detailed knowledge of the molecular basis of ALPS, a number of unexplained questions about the pathogenesis of the disease remain. Lymphomas have occurred in certain families with *APT1* mutations, and the malignant cells were found to carry the *APT1* mutation.⁷³ These findings suggest that a defect in Fas, together with additional unidentified abnormalities, can contribute to malignant lymphoid transformation. The majority of ALPS-associated autoimmune diseases primarily affect the hematopoietic system, and there is only a limited spectrum of autoantibodies found, suggesting that in the human population the role of Fas in self-tolerance is selective. In addition, studies of family members demonstrated that the same *APT1* mutation could produce a wide range of findings from clinically normal to ALPS.^{68,70,74} Family members with mutations affecting the intracellular domain of *Fas* have increased disease penetrance and morbidity when compared with those with mutations affecting the extracellular domains.⁷⁵ Rare patients with ALPS who have homozygous *APT1* mutations have a history of very early onset of disease and a more aggressive course.⁷⁶ This suggests that the amount of residual Fas function present in the different pedigrees may influence the severity and penetrance of the disease. A minority of patients with ALPS studied to

date have defective in vitro Fas-mediated apoptosis but do not have a mutation in *APT1*.⁶⁸ Mutations elsewhere in the Fas signaling pathway are being sought out in these patients. Taken together, ALPS defines the clinical spectrum of findings resulting from inherited mutations in the Fas receptor: lymphocyte accumulation, specific forms of autoimmunity, and an increased incidence of lymphoid malignancy. Significantly, defects in other cell types, such as hepatocytes, were not found, suggesting that there may be other death receptors in these tissues that can compensate for impaired Fas function. As in many other genetic diseases, the expression of clinical disease and laboratory abnormalities in each patient depends on the site of the mutation and additional genetic and epigenetic factors.

Evidence of alterations in the Fas apoptotic pathway in other autoimmune disorders is less well documented. Because of the Fas and Fas ligand abnormalities in the *lpr* and *gld* mouse models of SLE, mutations in these genes have been searched for in patients with SLE. In one such study, a single patient with a Fas ligand mutation similar to that seen in the *gld* mouse was identified. Interestingly, the clinical history of this patient revealed chronic lymphadenopathy reminiscent of ALPS.⁷⁷ Paradoxically, there is evidence that circulating activated T cells in certain autoimmune diseases, such as SLE, undergo increased spontaneous apoptosis.⁷⁸ This has been demonstrated to be the result of an increased sensitivity to the apoptotic signal provided by IL-10, and this process appears to be mediated through Fas.⁷⁹ Similar findings were also observed in lymphocytes obtained from patients with vasculitis. It is interesting to note that patients with ALPS have markedly elevated levels of circulating IL-10 that could reflect a compensatory mechanism in an attempt to control the lymphoproliferation.⁸⁰

There is some evidence that upregulation of Fas ligand and/or Fas expression on thyroid cells may play a role in autoimmune thyroiditis.^{81,82} This is hypothesized to result in thyrocyte suicide after self-engagement of Fas by Fas ligand. However, the level and functional role of Fas ligand expression by thyrocytes is controversial, and the contribution of Fas ligand from infiltrating T cells is difficult to rule out. As in mouse model systems, cell death by means of engagement of Fas appears to play a major role in hepatocyte death associated with viral hepatitis in humans.^{57,83} Hepatocytes express Fas, and the activation of cytotoxic T cells expressing Fas ligand in response to viral infection initiates T-cell mediated apoptosis of hepatocytes. There is recent evidence that release of soluble Fas ligand correlates with the severity of liver injury associated with hepatitis and as such may serve as a marker of disease severity.⁸⁴

There may also be a role for Fas as a negative regulator in some allergic diseases. In addition to undergoing spontaneous apoptosis, cultured eosinophils have been found to be susceptible to Fas-mediated apoptosis.⁸⁵ In patients with atopic dermatitis and inhalant allergies, spontaneous eosinophil apoptosis is impaired, but the mechanism of this effect is not clear.⁸⁶ Cytokines, such

as IL-3, IL-5, and GM-CSF, can inhibit Fas-induced eosinophil apoptosis,⁸⁷ and impaired eosinophil apoptosis has been implicated in tissue eosinophilia.⁸⁸ Two patients with hypereosinophilia have been described with decreased expression of Fas or a soluble Fas inhibitor,⁸⁹ and certain features shared with ALPS, such as increased CD4⁺CD8⁻ T cells, were present. However, patients with ALPS who had severe defects in Fas function do not generally develop eosinophilia, making it difficult to know whether Fas is absolutely required to regulate eosinophil homeostasis.

In HIV infection, peripheral T cells are more sensitive to Fas-induced apoptosis, but this is likely to reflect the state of immune cell activation rather than a specific effect of HIV.⁹⁰ Fas/Fas ligand interactions may play a role in bystander lymphocyte death because T cells exposed to HIV-infected macrophages undergo Fas-mediated apoptosis.^{91,92} However, the direct killing of virally infected T cells is not dependent on Fas signaling because lymphocytes from Fas-deficient patients with ALPS are equally sensitive to cell death after in vitro viral infection.⁹³

Certain malignant cells express Fas on their cell surface, and this may provide a mechanism to eliminate locally reactive lymphocytes.⁹⁴ Recently, a decoy molecule that resembles Fas and binds Fas ligand has been found to be produced by some colon and lung cancer cells.⁹⁵ This molecule can bind to Fas ligand, blocking the immune cytotoxic T-cell attack of the malignant cells. The clinical significance of these findings is not known, but these data suggest that tumors have adopted mechanisms that can block an immune response directed at the malignant cells. Multiple myeloma is a malignant disease in which an alternative mechanism linking Fas to malignant disease has been suggested. In this B-cell malignancy it appears that the normal Fas-mediated apoptotic pathway is defective, allowing the clonal plasma cell to develop immortality.⁹⁶ The basis for the defect in apoptosis can be related to mutations in Fas and/or the antiapoptotic effect of IL-6, a cytokine contributing to the growth of malignant cells in multiple myeloma.^{97,98}

THE FAS/FAS LIGAND SYSTEM IN DIAGNOSIS AND THERAPY

The interest in the Fas pathway, together with the availability of tests for soluble Fas and soluble Fas ligand, have stimulated investigation into the potential utility of these assays in a large array of human disorders. Overall, it appears that soluble Fas and Fas ligand are increased in clinical states of immune activation. As such, these tests do not appear to provide significant advantage over a variety of other nonspecific markers of immune activation. However, in certain circumstances, such as viral hepatitis and perhaps other organ-specific disorders, one or both assays may provide additional information regarding the extent of disease or response to therapy. At this time it is too early to predict whether these tests will prove to be clinically useful.

The powerful ability of Fas ligand to eliminate activated lymphocytes has prompted trials of Fas ligand therapy in a number of autoimmune disease models. Systemic administration of anti-Fas antibodies leads to fatal fulminant hepatitis in mice as a result of Fas-mediated hepatocyte apoptosis.⁹⁹ However, local administration of anti-Fas antibodies or delivery of Fas ligand by means of gene transfer at the site of inflammation does not appear to have these side-effects. In a human T-lymphotropic virus-1 transgenic model of inflammatory arthritis, as well as in collagen-induced arthritis, symptoms were alleviated in short-term studies with Fas ligand.^{100,101} Regression of arthritis was associated with apoptosis of both resident synovocytes and infiltrating mononuclear cells. Whether the toxic and proinflammatory effects of Fas ligand therapy can be overcome in the treatment of human disease represents a major challenge for the future.

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